Repetitive transcranial magnetic stimulation as an augmentative strategy for treatment-resistant depression, a meta-analysis of randomized, double-blind and sham-controlled study

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Abstract

Objective: Dozens of randomized controlled trials (RCTs) and meta-analyses have demonstrated the efficacy of repetitive transcranial magnetic stimulation (rTMS) for major depressive disorder (MDD) treatment, but there has not been a meta-analysis report which evaluates the efficacy and tolerability of rTMS used as an augmentative strategy for antidepressants in MDD treatment. We thus conducted this meta-analysis, aimed at clarifying whether rTMS enhances the efficacy of antidepressants for treatment-resistant depression (TRD).

Methods: We searched MEDLINE and Cochrane Central Register of Controlled Trials for RCTs for studying the efficacy of rTMS versus (vs) sham condition when combined with antidepressants in treatment-resistant depression, and screened the references of the previous meta-analysis about the rTMS for MDD treatment. Response rates and NNT were chose as the primary outcomes, and remission rates, change from baseline of HAMD scores, dropouts were used as secondary outcomes. For dichotomous data, an intention-to-treat analysis principle was applied; for continuous data, we calculated the standard mean difference between groups in a random-effect model. Sensitivity analysis was done to explore the source of heterogeneity and the factors which potentially impact the efficacy.

Results: Seven RCTs were finally included in the meta-analysis. The total sample size of 279 subjects, with 171 in the rTMS group and 108 were included in the sham group. The pooled response and remission rate for the rTMS and sham group was 46.6% and 22.1%, respectively; the pooled odds ratio (OR) was 5.12 [95% confidence interval (CI) 2.11-12.45, z=3.60, p=0.0003, and the associated number needed to treat (NNT) was 3.4. rTMS group achieved a significant reduction of HAMD score than the sham group, the pooled SMD of change from baseline was 0.86 [95%...
Confidence interval (CI) 0.57-1.15, z=5.75, p<0.0001). Because of the small number of included RCTs, sensitivity and subgroup analysis was not well conducted for the significant heterogeneity of RCTs in subgroup analysis. The dropouts in both groups were relatively low, indicating the high acceptability of rTMS.

**Conclusions:** For treatment-resistant MDD patients, an augmentative strategy of rTMS after the failure of medications significantly increases the antidepressive effect, and rTMS was a safe strategy with relatively low adverse events and low dropout rate, suggesting that adjunctive rTMS is an effective intervention for MDD.

**Key words:** transcranial magnetic stimulation, depression, treatment-resistant

**Background**

Depression is a global severe disease. In a report of world health organization (WHO) [1], MDD ranked thirdly in global disease burden in 2004 and ranked firstly in moderate and high income countries. Unfortunately, even after all medications were tried, more than 30% of patients can not achieve a clinical response [2]; these patients, which are called treatment-resistant depression (TRD) patients, exerted extremely severe burden on themselves and their families. So the treatment of TRDs has become one of the most important and pressing problem in psychiatry. Recently, with the development of neurobiology and neuroimaging, we are able to treat some TRDs with some physical method, such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDcS). Among these methods, rTMS is the most promising due to its high efficacy and acceptability (low adverse effects) [3].

rTMS utilizes an electromagnet that generates local magnetic field pulses to modulate brain functions. It is believed that rTMS modulates the activity of local neural circuits by suppressing neurons with the frequency of electromagnetic field lower than 1Hz while stimulating neurons with the frequency higher than 5Hz in the cerebral cortex [4, 5], whereby rebuilding the balance of different brain areas and alleviating the symptoms of different psychiatric disorders. rTMS was first used in MDD treatment in 1995 by George et al [6], and numerous literatures about the efficacy of rTMS on MDD have been published afterwards. For MDD patients, high frequency stimulation focused on the left dorsal lateral prefrontal cortex (LDLPFC) and low frequency on the right dorsal lateral prefrontal cortex (RDLPFC) were most commonly used [3].

At present, several meta-analyses [7-22] have indicated that rTMS is effective for MDD patients. But most studies had focused on both treatment-resistant and non-resistant patients and had chosen continuous data, namely, change from baseline of HAMD or MADRS scores as the primary outcome except for the study reported by Lam et al [15], which focused on the treatment-resistant depression patients and chose dichotomous data, such as response rates and remission rates as the primary outcomes. The former kind of data tends to reserve the information of each RCT as much as possible, while the latter is easier for doctors and patients to understand. Nevertheless, the study by Lam et al contained unexpected high heterogeneity, and included RCTs that designed rTMS as either monotherapy or augmentation to antidepressants, which may be on suspicion of mixing apples and oranges together.

In view of the above disadvantages of the previous meta-analyses, we designed this meta-analysis focused on RCTs which studied the efficacy of rTMS used as an augmentative strategy for antidepressants in treatment-resistant depression.
Response rates and NNT were chosen as the primary outcomes. The baseline of HAMD scores, remission rates and dropout rates were selected as secondary outcomes. We synthesized the data of RCTs meeting the inclusion criteria in order to reduce the complexity and contradictions of different RCTs with relatively small samples collected from available databases and literatures. Sensitivity and subgroup analyses were conducted further to explore the source of heterogeneity and potential factors which may influence the efficacy of rTMS on TRD.

Methods

Search strategy

We identified articles for inclusion in this meta-analysis by:

1. Searching MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) from 1 January 1995 to 30 November 2013, using the key words “transcranial magnetic stimulation”, “depress*”, “augment*”, “combin*”, “adjunctive”, “resistant” and “refractory”. We restricted the article type to “randomized controlled trial” and the language to “English”.

2. Searching the references of all the previous relevant meta-analyses [7-22] focused on the efficacy of rTMS for MDD published earlier than 30 November 2013, as well as of all included RCTs.

The search procedures are described in details in supplementary materials.

Inclusion criteria and exclusion criteria

Studies included in this meta-analysis should satisfy the following criteria:

1. Study validity: random allocation; double-blind (i.e. both patients and outcome raters were blind to the allocation); sham-controlled; rTMS was used as augmentation to antidepressants;

2. Sample characteristics: subjects should be 18-75 years old with a diagnosis of MDD according to DSM-IV or ICD-10, comorbidity of psychotic symptoms was excluded;

3. Efficacy evaluation and outcome reporting: efficacy should be rated by HAMD (17- or 21-items) or MADRS, and data are reported in a continuous (means and standard deviations (SDs) of pre- and post- treatment HAMD or MADRS scores) or dichotomous (response, remission and dropout rates) form able to be synthesized in this meta-analysis.

4. Articles should be published in English.

Studies were excluded if they were:

1. Non-RCT design, such as open trials;

2. Subjects were limited to a specific type of MDD patients, such as postpartum MDD, old MDD or secondary depression (i.e., vascular depression);

3. Sample size smaller than 5 in either rTMS or sham group;

Data extraction
(1) Sample characteristics: mean age, gender, diagnosis criteria and definition of resistancy;

(2) rTMS-related: frequency, intensity, location, treatment strategy (number of sessions, duration of each stimulation and duration of each interval) and total pulses;

(3) Drug-related: drug strategy (standardized or non-standardized), washout, types and dosages of each type;

(4) Primary outcome measure: number of responders based on the RCTs’ primary efficacy measure (defined as ≥50% reduction in post-treatment on the HAMD or MADRS scores) at the end of blinded treatment;

(5) Secondary outcome measure: number of remitters based on the RCTs’ primary efficacy measure (e.g. 17- or 21-item HAMD scores ≤7 or ≤8, respectively, or MADRS scores ≤6) at the end of blinded treatment, or the means and SDs of change of 17 or 21-item HAMD or MADRS scores;

(6) Acceptability of treatment: number of dropouts in rTMS and sham groups in each RCT.

Data synthesis and analysis

This meta-analysis was conducted according to the Cochrane Handbook for Systematic Reviews of Intervention [23], all statistic work were performed by Review Manager 5.2 and Excel 2007.

We used a random-effect model because the efficacy of rTMS between different RCTs was assumed to be varied considerably. This model endows small-sample studies with higher weight and leads to a relatively conservative result [24]. For dichotomous data, if available, an intention-to treat analysis was selected. In other words, we included all dropouts after randomization, because this is closer to clinical practice. When dropouts were excluded for efficacy assessment in any individual RCT (e.g. subjects who never returned for assessment after randomization), they were considered as non-responders. We calculated the pooled OR of response rate and associated NNT. As reported in other studies, an NNT≤10 was considered as clinically meaningful because such a treatment difference would be regularly encountered in clinical practice [25]. For continuous data, we calculated standardized mean difference (SMD) of the baseline HAMD or MADRS scores and change from baseline of HAMD or MADRS scores after the blinded treatment between active rTMS and sham groups. When a study had more than 2 groups, the data of different active rTMS groups were combined together as one group (the data were combined only when the active groups did not show significant difference, if they did, the RCT were excluded).

Heterogeneity was assessed by chi-square and I-square statistics [26], which is considered to be an indicator of study heterogeneity when p value for $\chi^2$ was lower than 0.1 or when $I^2$ was higher than 35%. Sensitivity and subgroup analysis were conducted to determine the potential factors, such as sessions ($\leq10$ or $>10$), intensity ($\leq100\%$ or $>100\%$) or total pulses ($\leq10000$ or $>10000$), which may influence the antidepressant efficacy of rTMS. Nevertheless, because the number of included RCTs was relatively small, the heterogeneity of studies in subgroup analysis was considerably high, which lowered the reliability of the results. Finally, we used funnel plot and visual inspection to examine the publication bias.
Results

Literature search and screening

All the 7 RCTs [27-33] included in this meta-analysis were identified by electronic database searching, and the hand searching of bibliographies of previous meta-analyses did not result in additional studies available for data synthesis; two RCTs[34, 35] on rTMS’s augmentative effect for TRD obtained by hand searching were excluded, because the data described in these two reports are unable to synthesize in this study. The process of literature search and screening was shown in Figure 1 and a detailed description of the process was available in supplementary material.

Included studies: main characteristics

All included RCTs [27-33] used HAMD as a primary outcome measurement. They all mentioned randomization, while no one described the scheme of allocation concealment in details. Three studies [30, 31, 33] reported how they guaranteed the blindness of the patients and the efficacy raters, while the other 4 RCTs [28, 29, 32] just mentioned “the patients and raters did not know which group they were allocated”. The risk of bias table was shown in Figure 2. The main characteristics of included RCTs were described in Table 1.

Response rates

Six RCTs had reported qualified data about response rates. As a whole, 68/146 (46.6%) and 15/84 (22.1%) subjects in the active or sham rTMS groups were classified as responders, respectively. The pooled OR was 5.12 (95% CI 2.11-12.45, z=3.60, p=0.0003), implying a significant difference favoring the active rTMS group (Figure 3). The risk difference translated into NNT was 3.4, namely, one patient would get clinical response in every 3.4 patients being treated.

Heterogeneity between RCTs did not exceed that expected by chance (χ²=6.09, p=0.30, I²=18%), meaning that the variance among the effect sizes was no greater than that expected by sampling error. For the associated Funnel Plot, please refer to the Supplementary Material.

Change from baseline of HAMD scores

Data relating to change from baseline of HAMD scores were available from 6 RCTs, with a total of 126 and 87 subjects in the active rTMS and sham group, respectively. The pooled SMD was 0.86 (95% CI 0.57-1.15, z=5.75, p<0.00001), indicating the superiority of active rTMS in alleviating depression severity compared with sham rTMS (Figure 4).

Heterogeneity between RCTs did not exceed that expected by chance (χ²=2.67, p=0.75, I²=0%), indicating that the data were reasonably appropriate for synthesis. The associated Funnel Plot was approximately symmetrical. For the associated funnel plot, please refer to the Supplementary Material.

Acceptability of treatment

All the 7 studies included in this meta-analysis reported the data of dropouts. In total, 9/171 (5.7%) and 5/108 (5.04%) dropped after the blinded treatment in the active rTMS and sham groups, respectively. The dropout rates in both groups were relatively low and had no significant difference [risk difference (RD)=0.01, 95% CI -0.04-0.07, z=0.48, p=0.63] (because there were no dropouts in two RCTs[29, 30],
to enroll the data of the two studies, we chose RD rather than OR), indicating the relatively low adverse effect and high acceptability of rTMS. Additionally, the side effects reported by patients were presented in Table 1. The most frequent reported side effects were mild headache and discomfort in stimulation location, the headache and discomfort were commonly transient and did not differ significantly between groups, implying the safety of rTMS. For the associated forest plot and funnel plot, please refer to the Supplementary Material.

Remission rate

Only 2 RCTs [30, 31] reported the number of remitters at the end of blinded rTMS treatment, both of them found a significant difference between the active and sham groups in achieving remission. For the small number or RCTs, data were not synthesized. For detailed description, please refer to the Supplementary Material.

rTMS vs sham group: baseline depression severity

No significant difference were observed in baseline severity between active and sham rTMS groups, the pooled SMD was -0.09 [95% CI -0.34-0.17, \( z=0.66, p=0.51 \)], indicating that the two groups are comparable at baseline and baseline depression severity cannot be a confounding factor of the efficacy. For the associated forest plot and funnel plot, please refer to the Supplementary Materials.

Sensitivity and subgroup analyses

We tried to carry out sensitivity and subgroup analyses to explore the potential confounding factors, such as number of sessions, intensity and total pulses, and drug strategy (standardized or non-standardized). However, because the number of included studies is relatively low and the heterogeneity between RCTs in subgroups were very high, the preplanned subgroup analyses were finally abandoned to avoid the misleading results. For detailed description, please refer to the Supplementary Materials.

Follow-up data

Five studies implemented open intervention after the blinded treatment. In these follow-up studies, patients in sham groups who did not achieve response in blinded treatment were enrolled to receive active rTMS treatment, the efficacy of these “subsequent rTMS treatment” were reported in these studies, but the data measuring the median- and long-term efficacy of rTMS treatment were not available. Thus it is unclear how long the efficacy of rTMS treatment can persist.

Discussion

To our knowledge, this is the first meta-analysis exploring the efficacy of augmentative rTMS for TRD. We included 7 RCTs and our results demonstrated that rTMS is significantly superior to sham condition in TRD treatment, the pooled OR was 5.12 (95% CI 2.11-12.45, \( z=3.60, p=0.0003 \)), and the associated NNT was 3.4, indicating a relatively high efficacy of rTMS in TRD treatment. Moreover, our results showed that patients receiving rTMS treatment achieved significantly greater decrease in HAMD scores than those who receiving sham condition (SMD= 0.97, 95% CI 0.64-1.31, \( z=6.00, p<0.00001 \)). Additionally, our results manifested that the baseline depression severity and dropout rates of the two groups did not differ significantly.
Although more than 10 meta-analyses about the efficacy of rTMS on depression had been published, there was only one meta-analysis [15] focused on the treatment-resistant patients. Nevertheless, the study by Lam et al found a relatively high heterogeneity between the included RCTs, and this may be due to their enrollment of studies which used rTMS either as monotherapy or augmentation to antidepressants. Our results overcome the weakness by limiting the included studies only to the RCTs using rTMS as an augmentative strategy. For other meta-analyses, most of them had chosen change from baseline of HAMD scores or end-point HAMD scores as the primary outcome assessment, this may facilitate reserving the information of each individual study, but the outcomes of these studies are usually complicated and not easy for doctors and patients to understand. In this study, we provided an easily understood result by choosing response rate and NNT as the primary outcomes.

Despite the advantages aforementioned, our study has some limitations. Firstly, the strict inclusion criteria in this study may help to reduce heterogeneity and enhance the reliability of our results, but it may also limit our results only suitable for the condition of augmentative rTMS for TRD patients, thus we cannot know the efficacy of rTMS used as monotherapy for TRD patients or used as augmentative strategy for non-resistant MDD patients from the results of our study. However, that is not we intended to know and previous meta-analyses [10, 15, 20] had told us the answers to the above questions. Secondly, the quality of included RCTs is relatively low. Like other relevant meta-analyses [10, 15], most included RCTs in this study did not report the method of allocation concealment and implementation and maintenance of blinding, which may lower the scoring of study quality. Thirdly, as mentioned in other meta-analyses and RCTs, the sham condition used in most studies cannot fully eliminate the placebo effect [3], because some patients receiving rTMS treatment can perceive the vibration of electromagnetic coil while the patients in the sham group cannot experience the effect. Moreover, the “5-cm” location method is often criticized for its inaccuracy [36, 37], and it is unknown where is the exact stimulated location. Fourth, the follow-up duration of included studies was relatively low, and most studies designed open rTMS treatment in the follow up period. These factors make it impossible to estimate the median- or long-term naturalistic efficacy of rTMS. Fifth, as the number of included RCTs was relatively low, the predetermined subgroup analyses were finally not successfully conducted for the high heterogeneity. Therefore, it is unclear whether the intensity, frequency and total pulses of rTMS and drug strategy had contributed to the accuracy of the present results, and it should be settled by future studies.

In conclusion, our study showed that augmentative rTMS was significantly superior to sham condition in TRD treatment, and the two groups did not differ significantly in dropout rates or side effects, indicating the advantage of rTMS in the efficacy and acceptability for clinical treatment of TRD. As the number of included RCTs was relatively low and the heterogeneity of RCTs in subgroup analysis is higher than expected by chance, we did not explore the potential confounding factors which may influence the effect of rTMS. Future studies should have more rigid design, such as reporting the method of allocation concealment and blinding in details, carrying out longer non-interventive follow-up to make clear of long-term efficacy of rTMS, and improving the design of sham condition to alleviate placebo effect further. Additionally, combination with neuroimaging technique for identifying the best stimulation location is expected.

Authors’ contributions
Bangshan Liu participated in the study design, developed the meta-analysis method, and drafted the manuscript. Yan Zhang co-developed the meta-analysis method, participated in the literature search, study selection, extraction of data and performed the statistic analysis. Li Zhang participated in the literature search, study selection and data extraction. Lingjiang Li participated in the study design and coordination, provided clinical expertise on rTMS and MDD and helped to draft the manuscript. All authors read and approved the final manuscript.

Conflict of interest
The authors declare that they have no competing interests.

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References:


resistant depression. In: Neuropsychiatric Disease and Treatment. vol. 9; 2013: 397-401.


<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size (n)</th>
<th>Diagnosis</th>
<th>TRD definition</th>
<th>Medication regimen</th>
<th>rTMS parameters</th>
<th>Outcome assessment</th>
<th>Follow-up?</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garcia-Toro et al, 2001 [28]</td>
<td>17 18</td>
<td>DSM-IV MDD</td>
<td>Failed 2 or more ADs, 6 weeks minimum</td>
<td>continue current treatment</td>
<td>20 90 10 12000</td>
<td>HAMD-21</td>
<td>2w of an open trial</td>
<td>Scalp discomfort and slight headaches</td>
</tr>
<tr>
<td>Rossini et al, 2005 [31]</td>
<td>18 17 19</td>
<td>DSM-IV MDD &amp; ≥26 in HAMD-21</td>
<td>Failed 2 or more ADs, 6 weeks minimum</td>
<td>continue current treatment</td>
<td>15 100 10 6000</td>
<td>HAMD-21</td>
<td>3w of follow up</td>
<td>Mild headache; discomfort at the site of stimulation</td>
</tr>
<tr>
<td>Garcia-Toro et al, 2006 [29]</td>
<td>10 10 10</td>
<td>DSM-IV MDD</td>
<td>Failed 2 or more ADs, 1 month minimum</td>
<td>continue current treatment</td>
<td>20,1 110 10 12000</td>
<td>HAMD-21</td>
<td>2w of follow up</td>
<td>Scalp discomfort and headaches</td>
</tr>
<tr>
<td>Bretlau et al, 2008 [32]</td>
<td>22 23</td>
<td>DSM-IV MDD</td>
<td>Failed 2 or more ADs, 6 weeks minimum</td>
<td>Escitalopram from 10mg/d to 20mg/d</td>
<td>8 90 15 19200</td>
<td>HAMD-17</td>
<td>9w of follow up</td>
<td>Reduced sleep length and greater concentration difficulties (sham group)</td>
</tr>
<tr>
<td>Martinot et al, 2010 [33]</td>
<td>16 18</td>
<td>DSM-IV-R MDD &amp; ≥18 in MADRS &amp; ≥16 in HAMD</td>
<td>Failed 2 or more ADs, 4 weeks minimum</td>
<td>minimal and stable dosage of previous treatment</td>
<td>10 90 10 16000</td>
<td>HAMD-21</td>
<td>N</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Bakim et al, 2012 [30]</td>
<td>12 12 11</td>
<td>DSM-IV MDD &amp; ≥18 in MADRS &amp; ≥20 in HAMD</td>
<td>Failed 2 or more ADs, 6 weeks minimum</td>
<td>continue current treatment</td>
<td>20 80 30 24000</td>
<td>HAMD-17</td>
<td>N</td>
<td>Mild headache and mild discomfort</td>
</tr>
<tr>
<td>Chen et al, 2013 [27]</td>
<td>10 11</td>
<td>DSM-IV MDD &amp; ≥18 in HAMD-17</td>
<td>Failed 2 or more ADs, 6 weeks minimum</td>
<td>continue current treatment, stable dose</td>
<td>20 90 10 8000</td>
<td>HAMD-17</td>
<td>9w of follow up</td>
<td>Not mentioned (1 dropouts for unspecific somatic complaints, sham group)</td>
</tr>
</tbody>
</table>
Figure 1

Studies identified through MEDLINE (n=18)

Studies identified through previous meta-analyses (n=50)

Studies after duplicates removed (n=27)

Studies included after titles and abstracts screening (n=9)

Studies included (n=7)

Studies excluded in titles and abstracts

Studies included after duplicates removed (n=9)

Studies excluded in full text screening

Studies included after full article screened (n=7)
Figure 2: Bias assessment for different aspects of the study.

- Random sequence generation (selection bias): Low risk of bias.
- Allocation concealment (selection bias): Unclear risk of bias.
- Blinding of participants and personnel (performance bias): Low risk of bias.
- Blinding of outcome assessment (detection bias): Unclear risk of bias.
- Plausibility of the sham condition: Low risk of bias.
2.6 intention-to-treat analysis of response

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>active rTMS Events</th>
<th>Total</th>
<th>sham rTMS Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Difference M-H, Random, 95% CI</th>
<th>Risk Difference M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakim 2012</td>
<td>18</td>
<td>23</td>
<td>2</td>
<td>12</td>
<td>15.4%</td>
<td>0.62 [0.35, 0.89]</td>
<td></td>
</tr>
<tr>
<td>Chen 2013</td>
<td>7</td>
<td>10</td>
<td>8</td>
<td>11</td>
<td>9.8%</td>
<td>-0.03 [-0.41, 0.36]</td>
<td></td>
</tr>
<tr>
<td>Garcia-Toro 2001</td>
<td>5</td>
<td>20</td>
<td>1</td>
<td>20</td>
<td>19.4%</td>
<td>0.20 [-0.01, 0.41]</td>
<td></td>
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<tr>
<td>Garcia-Toro 2006</td>
<td>4</td>
<td>20</td>
<td>0</td>
<td>10</td>
<td>19.2%</td>
<td>0.20 [-0.01, 0.41]</td>
<td></td>
</tr>
<tr>
<td>Martinot 2010</td>
<td>18</td>
<td>36</td>
<td>3</td>
<td>14</td>
<td>15.4%</td>
<td>0.29 [0.02, 0.56]</td>
<td></td>
</tr>
<tr>
<td>Rossini 2005</td>
<td>16</td>
<td>37</td>
<td>1</td>
<td>17</td>
<td>20.8%</td>
<td>0.37 [0.18, 0.57]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>68</td>
<td>146</td>
<td>84</td>
<td>100.0%</td>
<td></td>
<td>0.29 [0.15, 0.44]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.02$; $\chi^2 = 10.24$, df = 5 (P = 0.07); $I^2 = 51$

Test for overall effect: $Z = 3.96$ (P < 0.0001)

Figure 3
Figure 4
2.18 Meta-analysis of active rTMS versus sham condition used as an augmentative strategy for antidepressants for treatment-resistant depression.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>active rTMS Mean</th>
<th>active rTMS SD</th>
<th>active rTMS Total</th>
<th>sham rTMS Mean</th>
<th>sham rTMS SD</th>
<th>sham rTMS Total</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
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<tr>
<td>Bakim 2012</td>
<td>12.69</td>
<td>5.96</td>
<td>23</td>
<td>6.08</td>
<td>5.83</td>
<td>12</td>
<td>15.4%</td>
<td>[0.34, 1.84]</td>
<td>[0.36, 1.60]</td>
</tr>
<tr>
<td>Bretlau 2008</td>
<td>8.9</td>
<td>3.22</td>
<td>22</td>
<td>5.6</td>
<td>3.4</td>
<td>23</td>
<td>22.3%</td>
<td>[0.36, 1.60]</td>
<td>[0.36, 1.79]</td>
</tr>
<tr>
<td>Chen 2013</td>
<td>13.9</td>
<td>1.37</td>
<td>10</td>
<td>12.6</td>
<td>1.36</td>
<td>10</td>
<td>9.9%</td>
<td>[-0.02, 1.84]</td>
<td>[0.36, 1.79]</td>
</tr>
<tr>
<td>Garcia-Toro 2001</td>
<td>7.05</td>
<td>5.66</td>
<td>17</td>
<td>1.77</td>
<td>3.78</td>
<td>18</td>
<td>16.8%</td>
<td>[0.36, 1.79]</td>
<td>[0.36, 1.79]</td>
</tr>
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<td>Garcia-Toro 2006</td>
<td>7.05</td>
<td>7.3</td>
<td>20</td>
<td>1.5</td>
<td>5.9</td>
<td>10</td>
<td>13.8%</td>
<td>[0.36, 1.79]</td>
<td>[0.36, 1.79]</td>
</tr>
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<td>Martinot 2010</td>
<td>15.5</td>
<td>10.9</td>
<td>34</td>
<td>10.5</td>
<td>12.3</td>
<td>14</td>
<td>21.8%</td>
<td>[0.36, 1.79]</td>
<td>[0.36, 1.79]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>126</td>
<td>87</td>
<td>100.0%</td>
<td>0.86</td>
<td>[0.57, 1.15]</td>
<td>[0.57, 1.15]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.67$, df = 5 ($P = 0.75$); $I^2 = 0$

Test for overall effect: $Z = 5.75$ ($P < 0.00001$)

Favours [sham condition] Favours [active rTMS]

-2 -1 0 1 2
2.20 dropouts in treatment-resistant depression

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>active rTMS</th>
<th>sham rTMS</th>
<th>Weight</th>
<th>Risk Difference M-H, Random, 95% CI</th>
<th>Risk Difference M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakim 2012</td>
<td>0</td>
<td>23</td>
<td>0</td>
<td>12 20.5%</td>
<td>0.00 [-0.12, 0.12]</td>
</tr>
<tr>
<td>Bretlau 2008</td>
<td>3</td>
<td>25</td>
<td>1</td>
<td>24 12.9%</td>
<td>0.08 [-0.07, 0.23]</td>
</tr>
<tr>
<td>Chen 2013</td>
<td>0</td>
<td>10</td>
<td>1</td>
<td>11 5.8%</td>
<td>-0.09 [-0.31, 0.13]</td>
</tr>
<tr>
<td>Garcia-Toro 2001</td>
<td>3</td>
<td>20</td>
<td>2</td>
<td>20 7.0%</td>
<td>0.05 [-0.15, 0.25]</td>
</tr>
<tr>
<td>Garcia-Toro 2006</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>10 15.0%</td>
<td>0.00 [-0.14, 0.14]</td>
</tr>
<tr>
<td>Martinot 2010</td>
<td>2</td>
<td>36</td>
<td>0</td>
<td>14 19.7%</td>
<td>0.06 [-0.07, 0.18]</td>
</tr>
<tr>
<td>Rossini 2005</td>
<td>1</td>
<td>37</td>
<td>1</td>
<td>17 19.1%</td>
<td>-0.03 [-0.16, 0.09]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>171</td>
<td>108</td>
<td>100.0%</td>
<td>0.01 [-0.04, 0.07]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>9</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.77$, df = 6 ($P = 0.84$); $I^2 = 0\%$
Test for overall effect: $Z = 0.48$ ($P = 0.63$)
Review Manager 5.1
Additional files provided with this submission:

Additional file 1: Supplementary material.doc, 734K
http://www.biomedcentral.com/imedia/1105986509129052/supp1.doc